

## Acetaminophen attenuates rhabdomyolysis-induced renal failure

Boutaud *et al.*, *Proc Natl Acad Sci USA* 2010; **107**: 2699–2704; doi:10.1073/pnas.0910174107

Release of myoglobin or hemoglobin into the circulation due to muscle injury or hemolysis can cause multiple problems, including renal failure. When these hemoproteins are released from the reducing environment of cells, the ferrous heme can be oxidized to the ferric state, conferring peroxidase activity to the hemoproteins. Consequently, hemoproteins can reduce hydroperoxides, such as hydrogen peroxide and lipid hydroperoxides, in a process that further oxidizes the hemoprotein to the ferryl state. Indeed, previous work suggests that generation of radical species by the heme redox cycling between ferric and ferryl states is responsible for the lipid peroxidation, and thus, the oxidative injuries associated with rhabdomyolysis, subarachnoid hemorrhage, and hemolysis. The coupling of a peroxidase-generated radical to lipid oxidation also occurs in the prostaglandin H<sub>2</sub> synthases (PGHSs) that catalyze oxygenation of arachidonic acid. Acetaminophen inhibits PGHSs by blocking formation of the catalytic tyrosyl radical. The analogy between the peroxidase catalytic cycle of PGHSs and the pseudoperoxidase activity of myoglobin and hemoglobin led Boutaud *et al.* to postulate that acetaminophen could prevent the peroxidation by these hemoproteins. They first demonstrated *in vitro* that acetaminophen inhibited hemoprotein-induced lipid peroxidation by reducing ferryl heme to its ferric state and quenching globin radicals. Heme-to-protein cross-linking is a more cytotoxic form of myoglobin that is generated at low pH, and *in vitro*, they also found that acetaminophen prevented both oxidative modifications and myoglobin cross-linking. More importantly, when rhabdomyolysis was induced in rats, pretreatment with acetaminophen so that the plasma concentrations were within the therapeutic range resulted in marked reduction of lipid peroxidation and improved kidney function, as shown in the concentration of plasma creatinine and the visual examination of the kidneys (Figure).

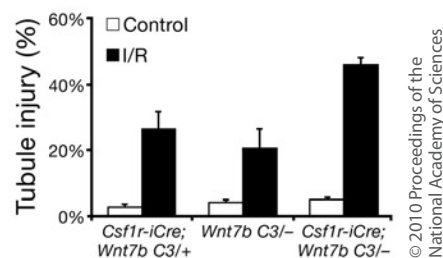
Thus, acetaminophen at therapeutic plasma concentrations significantly decreased oxidant injury in the kidney, improved renal function, and reduced renal damage after rhabdomyolysis. In

addition, the study suggests other potential therapeutic applications for acetaminophen in diseases involving hemoprotein-mediated oxidative injury.

Juan Oliver

## Macrophage Wnt7b is critical for kidney repair

Lin *et al.*, *Proc Natl Acad Sci USA* 2010; **107**: 4194–4199; doi:10.1073/pnas.0912228107

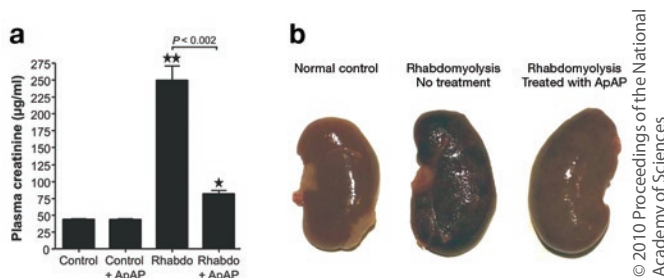


Deletion of Wnt7b in macrophages prevents normal repair and regeneration of the kidney following ischemia/reperfusion (I/R) injury. Quantification of tubular injury 7 days after transient ischemic injury in appropriate control mice (left and middle bars) and in mice with deletion of macrophage Wnt7b.

A substantial body of literature on several organs indicates that macrophages are important regulators of repair from injury. Wnt ligands and their receptors are also involved in tissue repair, and Wnt from macrophages was found to contribute to organogenesis. Lin *et al.* examined whether the canonical Wnt pathway was activated during kidney injury, and if so, whether it played a role in repair and regeneration. They induced transient ischemic injury in the kidneys of Wnt pathway reporter mice and found that there was marked upregulation of the Wnt pathway response 5 days after injury. Interestingly, this response was limited to interstitial cells and epithelial cells but not macrophages. To determine which molecular components of the Wnt pathway may be involved in the response to injury, the authors examined control and injured kidneys for mRNAs of ligands (Wnts), receptors (Fzds), and coreceptors (Lrp5 and Lrp6) and learned that several ligands (*Wnt2*, *2b*, *4*, *5a*, *7b*, *10a*) were upregulated. By isolating proximal tubular cells and renal macrophages, they found that macrophages were the likely source of Wnt ligands to which the epithelial cells responded and that *Wnt7b* was the likely critical ligand. To directly test whether macrophage Wnt ligands were involved in repair, they ablated macrophages *in vivo* and found that this caused a marked reduction of the activation of the Wnt pathway. To directly examine the role of Wnt7b from macrophages, they selectively deleted *Wnt7b* in these cells with Cre-Lox technology. As shown in the Figure, this resulted in markedly retarded repair after injury.

Thus, these results indicate that repair of damaged kidney tubules is mediated by an influx of macrophages that produce Wnt7b and signal locally to intact kidney epithelial progenitors.

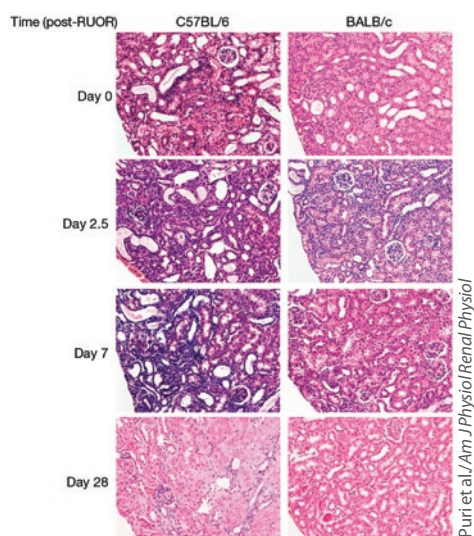
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(a) Effect of treatment with acetaminophen on plasma creatinine during rhabdomyolysis. (b) Visual examination of a representative kidney from a normal rat (left), a rat with rhabdomyolysis (middle), and a rat with rhabdomyolysis treated with acetaminophen (ApAP) (right).

## Genetic background modulation of the kidney's response to UUO

Puri *et al.*, *Am J Physiol Renal Physiol* 2010; **298**: F1024–F1032; doi:10.1152/ajprenal.00384.2009



Representative hematoxylin- and eosin-stained sections from C57BL/6 and BALB/c mice at various times following release of 6 days of right ureter obstruction (RUOR).

Although the kidney has a remarkable capacity to recover from injury, many kidney diseases inexorably progress to end-stage renal disease. The morphological hallmark under these conditions is the progressive substitution of the normal renal parenchyma by fibrotic tissue. Hence, the mechanisms responsible for renal fibrosis generate great interest.

The unilateral ureteral obstruction (UUO) model has been widely used to study renal fibrosis, as it offers several advantages over bilateral renal diseases, and it can be used in a transient manner, thus allowing analysis of renal repair from injury. In a recent publication, Puri *et al.* examined whether the genetic background of mouse strains frequently used in the laboratory affected the response of their kidneys to transient UUO. They used a reversible UUO model in C57BL/6 and BALB/c strains. They found that UUO of only 3 days' duration caused chronic kidney disease (assayed by blood urea nitrogen) in C57BL/6, but in marked contrast, BALB/c mice were resistant to development of chronic kidney disease with up to 10 days of UUO. Analysis of the histological features of a 6-day reversible UUO episode at various times (Figure) showed that at day 0 (6 days of UUO), as expected, there was considerable tubular injury with tubular dilatation, epithelial-cell flattening, and loss of brush border. In addition, interstitial inflammation was readily apparent and somewhat more prominent in kidneys from the C57BL/6 mice. However, at 7 days of post-reversible UUO, C57BL/6 mice had further inflammation, tubular atrophy, and interstitial fibrosis, whereas in BALB/c mice there was a gradual return toward normal histology. Histological differences were apparent up to 28 days of post-reversible UUO, with C57BL/6 mouse kidneys displaying persistent

mild interstitial inflammation associated with patchy areas of interstitial fibrosis around atrophic tubules, whereas BALB/c kidneys had a normal histological appearance.

These findings highlight the importance of the genetic background in analysis of the kidney's response to UUO and provide an exciting model to investigate the genetic basis of the kidney's recovery from transient UUO.

Juan Oliver

## Autophagy influences glomerular disease susceptibility and maintains podocyte homeostasis in aging mice

Hartleben *et al.*, *J Clin Invest* 2010; **120**: 1084–1096; doi:10.1172/JCI39492

Autophagy is increasingly being recognized as a mechanism to control cellular homeostasis under a large variety of stress situations. Autophagy is a pathway for removing cytosolic and membrane-associated proteins as well as entire cell organelles in an attempt to salvage cellular proteins during starvation and other types of tissue stress. As such, autophagy has been recognized to play a significant role in neurodegenerative as well as cardiac and liver diseases. In the kidney, increased autophagy has been shown during ischemia/reperfusion injury, transplant ischemia, and cisplatin and cyclosporine toxicity. In response to the associated cellular and tissue stress, autophagy is induced and may either serve as a cell survival mechanism or contribute to cell death. Hartleben *et al.* examined the potential role of autophagy in the function and survival of podocytes, as injury and loss of podocytes are leading factors of glomerular disease and renal failure. They report that podocytes exhibit an unusually high level of constitutive autophagy. Podocyte-specific deletion of autophagy-related gene 5 (*Atg5*) led to a glomerulopathy in aging mice that was accompanied by an accumulation of oxidized and ubiquitinated proteins, endoplasmic reticulum stress, and proteinuria. These changes resulted ultimately in podocyte loss and late-onset glomerulosclerosis. Analysis of pathophysiological conditions indicated that autophagy was substantially increased in glomeruli from mice with induced proteinuria and in glomeruli from patients with acquired proteinuric diseases. Further, mice lacking *Atg5* in podocytes exhibited strongly increased susceptibility to models of glomerular disease.

These findings highlight the importance of induced autophagy as a key homeostatic mechanism to maintain podocyte integrity. On the basis of these data, the authors postulate that constitutive and induced autophagy is a major protective mechanism against podocyte aging and glomerular injury. In addition, these results may shed some light on how sirolimus, an inhibitor of mTOR, may have beneficial effects in some glomerular diseases that are independent of the immune suppression. Sirolimus activates autophagy by inhibiting the kinase activity of mTOR, an effect that is independent of the immune suppression. If some of the beneficial effects of sirolimus turn out to be due to activation of autophagy, this mechanism may represent a putative target to ameliorate human glomerular disease and aging-related loss of renal function.

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